Association of sex with outcomes in patients undergoing percutaneous coronary intervention: a subgroup analysis of the global leaders randomized clinical trial

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Abstract: Importance: Women experience worse ischemic and bleeding outcomes after percutaneous coronary intervention (PCI). Objectives: To assess the association of sex with patient outcomes at 2 years after contemporary PCI and with the efficacy and safety of 2 antiplatelet strategies. Design, Setting, and Analysis: This study is a prespecified subgroup analysis of the investigator-initiated, prospective, randomized GLOBAL LEADERS study evaluating 2 strategies of antiplatelet therapy after PCI in an unselected population including 130 secondary/tertiary care hospitals in different countries. The main study enrolled 15 991 unselected patients undergoing PCI between July 2013 and November 2015. Patients had an outpatient clinic visit at 30 days and 3, 6, 12, 18, and 24 months after the index procedure. Data were analyzed between January 1, 2019, and March 31, 2019. Interventions: Eligible patients were randomized to either the experimental or reference antiplatelet strategy. Experimental strategy consisted of 1 month of dual antiplatelet therapy (DAPT) followed by 23 months of ticagrelor monotherapy, while the reference strategy comprised of 12 months of DAPT followed by 12 months of aspirin monotherapy. Main Outcomes and Measures: The primary efficacy end point was the composite of all-cause mortality and new Q-wave myocardial infarction at 2 years. The secondary safety end point was Bleeding Academic Research Consortium type 3 or 5 bleeding. Results: Of the 15 968 patients included in this study, 3714 (23.3%) were women. The risk of the primary end point at 2 years was similar between women and men (adjusted hazard ratio [HR], 1.00; 95% CI, 0.83-1.20). Compared with men, women had higher risk of Bleeding Academic Research Consortium type 3 or 5 bleeding (adjusted HR, 1.32; 95% CI, 1.04-1.67) and hemorrhagic stroke at 2 years (adjusted HR, 4.76; 95% CI, 1.92-11.81). At 2 years, there was no between-sex difference in the efficacy and safety of the 2 antiplatelet strategies. At 1 year, compared with DAPT, ticagrelor monotherapy was associated with a lower risk of bleeding in men (HR, 0.72; 95% CI, 0.53-0.98) but not in women (HR, 1.23; 95% CI, 0.80-1.89; P for interaction = .045). Conclusions and Relevance: Compared with men, women experienced a higher risk of bleeding and hemorrhagic stroke after PCI. The effect of 2 antiplatelet strategies on death and Q-wave myocardial infarction following PCI did not differ between the sexes at 2 years. Trial Registration: ClinicalTrials.gov identifier: NCT01813435.

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Association of Sex With Outcomes in Patients Undergoing Percutaneous Coronary Intervention

A Subgroup Analysis of the GLOBAL LEADERS Randomized Clinical Trial

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IMPORTANCE Women experience worse ischemic and bleeding outcomes after percutaneous coronary intervention (PCI).

OBJECTIVES To assess the association of sex with patient outcomes at 2 years after contemporary PCI and with the efficacy and safety of 2 antiplatelet strategies.

DESIGN, SETTING, AND ANALYSIS This study is a prespecified subgroup analysis of the investigator-initiated, prospective, randomized GLOBAL LEADERS study evaluating 2 strategies of antiplatelet therapy after PCI in an unselected population including 130 secondary/tertiary care hospitals in different countries. The main study enrolled 15 991 unselected patients undergoing PCI between July 2013 and November 2015. Patients had an outpatient clinic visit at 30 days and 3, 6, 12, 18, and 24 months after the index procedure. Data were analyzed between January 1, 2019, and March 31, 2019.

INTERVENTIONS Eligible patients were randomized to either the experimental or reference antiplatelet strategy. Experimental strategy consisted of 1 month of dual antiplatelet therapy (DAPT) followed by 23 months of ticagrelor monotherapy, while the reference strategy comprised of 12 months of DAPT followed by 12 months of aspirin monotherapy.

MAIN OUTCOMES AND MEASURES The primary efficacy end point was the composite of all-cause mortality and new Q-wave myocardial infarction at 2 years. The secondary safety end point was Bleeding Academic Research Consortium type 3 or 5 bleeding.

RESULTS Of the 15 968 patients included in this study, 3714 (23.3%) were women. The risk of the primary end point at 2 years was similar between women and men (adjusted hazard ratio [HR], 1.00; 95% CI, 0.83-1.20). Compared with men, women had higher risk of Bleeding Academic Research Consortium type 3 or 5 bleeding (adjusted HR, 1.32; 95% CI, 1.04-1.67) and hemorrhagic stroke at 2 years (adjusted HR, 4.76; 95% CI, 1.92-11.81). At 2 years, there was no between-sex difference in the efficacy and safety of the 2 antiplatelet strategies. At 1 year, compared with DAPT, ticagrelor monotherapy was associated with a lower risk of bleeding in men (HR, 0.72; 95% CI, 0.53-0.98) but not in women (HR, 1.23; 95% CI, 0.80-1.89; *P* for interaction = .045).

CONCLUSIONS AND RELEVANCE Compared with men, women experienced a higher risk of bleeding and hemorrhagic stroke after PCI. The effect of 2 antiplatelet strategies on death and Q-wave myocardial infarction following PCI did not differ between the sexes at 2 years.

TRIAL REGISTRATION ClinicalTrials.gov identifier: NCT01813435

Supplemental content

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There are sex-based differences in the pathophysiology, clinical presentation, and prognosis of coronary artery disease (CAD).[1,2] In vitro studies and small clinical studies have shown higher platelet activity, higher propensity to thrombosis, and more bleeding in women.[3,4] The short-term and long-term outcomes of CAD are usually better in men than women.[5]

Regardless of sex, percutaneous coronary intervention (PCI) has been established as an effective treatment in CAD with improved outcomes, which are comparable between sexes,[6,7] attributable to the use of second-generation drug-eluting stents (DES), imaging-guided and physiology-guided revascularization, and potent P2Y12 inhibitors.[8,9] Potent P2Y12 inhibitors increase the risk of bleeding, and the optimal strategy of antiplatelet therapy after PCI is still a matter of debate.[10] Notably, cessation of antiplatelet therapy is more common in women than men, and being a woman has been identified as an independent predictor for bleeding after PCI.[11]

In the GLOBAL LEADERS study, ticagrelor monotherapy following 1-month dual antiplatelet therapy (DAPT) with aspirin was safe but not superior to conventional DAPT in reducing the composite primary end point of all-cause mortality or core laboratory-adjudicated new Q-wave myocardial infarction (MI) in all-comer patients undergoing PCI.[12] Considering that the ischemic and bleeding risk of women undergoing PCI may differ from men, it follows that the safety and efficacy of long-term ticagrelor monotherapy after PCI may differ between the sexes. Therefore, we aimed to compare the 2-year outcomes between women and men undergoing contemporary PCI and to assess the association of sex with the efficacy and safety of antiplatelet strategy in the GLOBAL LEADERS study.

Key Points

Question What is the association of sex with patient outcomes after percutaneous coronary intervention?

Findings In this prespecified subgroup analysis of the GLOBAL LEADERS randomized clinical trial, there was no between-sex difference in the risk of 2-year all-cause mortality or new Q-wave myocardial infarction. The risks of bleeding and hemorrhagic stroke in women were higher than in men, and compared with dual antiplatelet therapy, ticagrelor monotherapy was associated with lower risk of bleeding at 1 year in men but not in women.

Meaning The effect of antiplatelet strategy on bleeding at 1 year may be different between the sexes.

Method

Study Design and Patient Population

This study is a prespecified subgroup analysis of the GLOBAL LEADERS study. The GLOBAL LEADERS study was an investigator-initiated, prospective, randomized, multicenter, multicontinental, open-label trial designed to evaluate 2 antiplatelet therapy strategies after PCI using uniformly bivalirudin and biolimus A9-eluting stents (Biomatrix) in an all-comers population with no restriction regarding clinical presentation, complexity of the lesions, or number of stents used.[12] Patients who needed oral anticoagulation therapy after PCI, had known overt major bleeding, were planned to undergo surgery within 12 months of PCI, or had severe hepatic impairment were not eligible for the study. The full inclusion and exclusion criteria are in the eMethods in Supplement 1. In the experimental strategy, patients received aspirin, 75 to 100 mg, once daily in combination with ticagrelor, 90 mg, twice daily for 1 month; followed by ticagrelor, 90 mg, twice daily alone for 23 months (irrespective of the clinical presentation). In the reference strategy, patients received aspirin, 75 to 100 mg, daily in combination with either clopidogrel, 75 mg, once daily in patients with stable CAD or ticagrelor, 90 mg, twice daily in patients with acute coronary syndrome (ACS) for 1 year; followed by aspirin, 75 to 100 mg, once daily alone for the following 12 months (from 12 to 24 months after PCI). The GLOBAL LEADERS study was approved by the institutional review board at each participating institution. All patients provided written informed consent. The study complied with the Declaration of Helsinki and Good Clinical Practice. An independent data and safety monitoring committee oversaw the safety of all patients. The formal trial protocols can be found in Supplement 2.

The main study enrolled 15 991 patients between July 2013 to November 2015 (eFigure 1 in Supplement 1). Because 23 patients withdrew consent and requested data deletion from the database, a total of 15 968 patients remained in the study. Patients had an outpatient clinic visit at 30 days and 3, 6, 12, 18, and 24 months after the index procedure. Electrocardiogram (ECG) was obtained at discharge, 3-month follow-up, and 2-year follow-up and during follow-up if there were suspected ischemic events or repeated revascularization. All ECGs were analyzed at the core laboratory (Cardialysis) by technicians who were blinded to the treatment assignments.

Study End Points

The primary end point of the present study was the composite of all-cause mortality and new Q-wave MI within 2 years after the index procedure. The survival status of the patients lost to follow-up or those who withdrew their consent was obtained through public civil registry. More than 99.95% of the vital status at 2 years were available in the study.[12] Minnesota classification was used to define the new Q-wave MI, which was centrally adjudicated by an independent ECG core laboratory. The secondary safety end point was investigator-reported Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding.[13] Additional secondary end points were the patient-oriented composite end points (POCE) and net adverse clinical events (NACE). Patient oriented composite end points were defined as all-cause mortality, any stroke (ischemic and hemorrhagic), any MI including periprocedural or spontaneous with ST-segment elevation myocardial infarction or non-ST-segment elevation myocardial infarction, and any revascularization (re-PCI or coronary artery bypass graft surgery [CABG] in target or nontarget vessel).[14] Net adverse clinical events were defined as POCE plus BARC type 3 or 5 bleeding. The composite end points were analyzed according to time-to-first-event analysis. Other end points included individual

Table 1. Baseline Clinical and Angiographic Characteristics According to Sex

Characteristic	No./Total No. (%)		*P* Value
	Men (n = 12 254)	Women (n = 3714)	
Baseline clinical characteristics			
Age, mean (SD), y	63.69 (10.22)	67.35 (10.09)	<.001
BMI, mean (SD)	28.17 (4.30)	28.25 (5.44)	.34
Type 2 diabetes	2972/12 247 (24.27)	1066/3710 (28.73)	<.001
Insulin-dependent diabetes	828/12 220 (6.78)	395/3701 (10.67)	<.001
Hypertension	8791/12 212 (71.99)	2924/3702 (78.98)	<.001
Hypercholesterolemia	8241/11 876 (69.39)	2527/3589 (70.41)	.25
Current smoker	3338/12 254 (27.24)	831/3714 (22.37)	<.001
Peripheral vascular disease	799/12 144 (6.58)	206/3678 (5.60)	.04
Chronic obstructive pulmonary disease	618/12 198 (5.07)	203/3698 (5.49)	.33
Previous major bleeding	70/12 241 (0.57)	28/3706 (0.76)	.26
Impaired renal function[a]	1348/12 187 (11.06)	823/3696 (22.27)	<.001
Previous stroke	306/12 235 (2.50)	115/3710 (3.10)	.05
Previous myocardial infarction	3009/12 216 (24.63)	701/3706 (18.92)	<.001
Previous percutaneous coronary intervention	4196/12 243 (34.27)	1025/3711 (27.62)	<.001
Previous coronary artery bypass grafting	781/12 246 (6.38)	162/3709 (4.37)	<.001
Clinical presentation			
Stable coronary artery disease	6491/12 254 (52.97)	1990/3714 (53.58)	.53
Unstable angina	1493/12 254 (12.18)	529/3714 (14.24)	.001
Non–ST-elevation myocardial infarction	2637/12 254 (21.52)	736/3714 (19.82)	.03
ST-elevation myocardial infarction	1633/12 254 (13.33)	459/3714 (12.36)	.13
Baseline angiographic characteristics			
Index PCI attempted, No.	12 187	3696	NA
No. of lesions treated at index PCI per patient, mean (SD)	1.33 (0.62)	1.28 (0.57)	<.001
Lesion treated at index PCI			
1 lesion	8952/12 136 (73.76)	2853/3682 (77.49)	<.001
2 lesions	2518/12 136 (20.75)	669/3682 (18.17)	
3 or more lesions	666/12 136 (5.49)	160/3682 (4.35)	
Lesion level[b]			
No. of lesion	16 140	4701	NA
Vessel treated			
Left main coronary artery	306/16 140 (1.90)	81/4701 (1.72)	.44
Left anterior descending artery	6599/16 140 (40.89)	2067/4701 (43.97)	
Left circumflex artery	4051/16 140 (25.10)	1026/4701 (21.83)	
Right coronary artery	5005/16 140 (31.01)	1485/4701 (31.59)	
Bypass graft	179/16 140 (1.11)	42/4701 (0.89)	
No. of stent per lesion, mean (SD)	1.19 (0.53)	1.19 (0.54)	.70
Biomatrix stent used	15 038/15 896 (94.60)	4377/4628 (94.58)	.99
Mean stent length, mean (SD), mm	24.99 (14.01)	24.20 (13.80)	.001
Mean stent diameter, mean (SD), mm	3.01 (0.47)	2.93 (0.45)	<.001
Direct stenting	5076/15 896 (31.93)	1608/4628 (34.75)	<.001
Bifurcation PCI	1960/16 140 (12.14)	556/4701 (11.83)	.94

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NA, not applicable; PCI, percutaneous coronary intervention.

[a] Estimated glomerular filtration rate of creatinine clearance of less than 60 mL/min per 1.73 m^2 based on the Modification of Diet in Renal Disease Formula.

[b] Calculated per lesion and analyzed with general or generalized linear mixed-effects models with a random effect for patients to account for multiple lesions treated within patients.

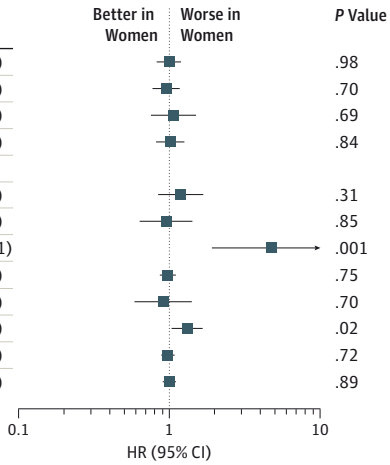
component of composite end point and definite stent thrombosis according to Academic Research Consortium (ARC) definition.[15]

Statistical Analysis

All the analyses were performed on the intention-to-treat population. Continuous variables are expressed as mean and standard deviation and were compared using independent *t* test. Categorical variables are presented as counts and percentage and were compared using χ^2 test. Lesion data were analyzed using mixed-effects models to account for multiple lesions treated within patients. Outcomes were analyzed based on the time-to-first-event analyses in which the repeated events were disregarded. Kaplan-Meier method was used to estimate the cumulative rates of events, and log-rank test was performed to examine the differences between groups. The association of sex with the outcomes was assessed in the unadjusted and adjusted Cox proportional hazards model. The covariables in the adjusted model included age, diabetes, renal impairment, presentation of ACS, prior MI, peripheral vascular disease, chronic obstructive pulmonary disease, and history of CABG, which were

Figure 1. Association of Sex With Clinical Outcomes at 2 Years After PCI

Outcomes at 2 y	Men, No. (%)[a] (n = 12 254)	Women, No. (%)[a] (n = 3714)	Unadjusted HR (95% CI)	*P* Value	Adjusted HR[b] (95% CI)	*P* Value
All-cause mortality or new Q-wave MI	477 (3.90)	176 (4.75)	1.23 (1.03-1.46)	.02	1.00 (0.83-1.20)	.98
All-cause mortality	346 (2.83)	131 (3.53)	1.26 (1.03-1.54)	.03	0.96 (0.78-1.18)	.70
New Q-wave MI	139 (1.15)	47 (1.29)	1.12 (0.81-1.56)	.49	1.07 (0.76-1.51)	.69
MI	380 (3.16)	118 (3.25)	1.03 (0.84-1.27)	.75	1.02 (0.82-1.27)	.84
Stroke						
Overall	113 (0.94)	49 (1.35)	1.45 (1.03-2.02)	.03	1.19 (0.85-1.69)	.31
Ischemic	97 (0.81)	34 (0.94)	1.17 (0.79-1.73)	.44	0.96 (0.64-1.43)	.85
Hemorrhagic	9 (0.08)	13 (0.36)	4.81 (2.05-11.25)	<.001	4.76 (1.92-11.81)	.001
Any revascularization	1188 (9.89)	344 (9.53)	0.96 (0.85-1.09)	.53	0.98 (0.87-1.11)	.75
Definite stent thrombosis	102 (0.84)	26 (0.71)	0.85 (0.55-1.30)	.45	0.92 (0.59-1.42)	.70
BARC 3 or 5 bleeding	223 (1.85)	109 (2.99)	1.63 (1.30-2.05)	<.001	1.32 (1.04-1.67)	.02
Patient-oriented composite end points	1665 (13.72)	516 (14.08)	1.03 (0.94-1.14)	.53	0.98 (0.89-1.09)	.72
Net adverse clinical events	1802 (14.84)	580 (15.82)	1.08 (0.98-1.18)	.12	1.01 (0.91-1.11)	.89



BARC indicates Bleeding Academic Research Consortium; HR, hazard ratio.

[a] Data were analyzed using the unadjusted Kaplan-Meier method.

[b] Adjusted by age, diabetes, renal impairment, presentation of acute coronary syndrome, prior myocardial infarction (MI), peripheral vascular disease, chronic obstructive pulmonary disease, and history of coronary artery bypass grafting.

selected based on prior knowledge of the association of these covariables with the outcomes.[16] Hazard ratios (HRs) and 95% confidence intervals were calculated.

The effect of experimental vs reference strategy on the outcomes was assessed separately in women and men in the unadjusted Cox model. The difference in the treatment effect between experimental vs reference strategy in women and men was assessed in the Cox model with the inclusion of main effect terms (sex and treatment strategy) and interaction term (sex × treatment strategy) for the outcome of interest.

Landmark analyses at 1 year were performed in accordance to the planned discontinuation of P2Y12 receptor inhibitor in the reference group. A 2-sided *P* value less than .05 was considered statistically significant. All analyses were performed in R, version 3.4.2 (the R Foundation).

Results

Baseline Clinical and Angiographic Characteristics

Of 15 968 patients enrolled in the GLOBAL LEADERS study between July 2013 and November 2015, 12 254 (76.7%) were men, and 3714 (23.3%) were women. Compared with men, women were older and had higher prevalence of diabetes, hypertension, and impaired renal function. Women were more likely to be nonsmokers, had lower prevalence of prior MI, and less likely to have had previous treatment with PCI and CABG (**Table 1**). The proportion of patients presenting with stable CAD were similar between men and women. Compared with men, women were more likely to present with unstable angina and non-ST-segment elevation myocardial infarction. Women had a lower number of lesions treated at the index procedure than men (Table 1). Mean stent length and mean stent diameter were lower in women than in men. Other angiographic characteristics were similar between both sexes.

Clinical Outcomes According to Sex

At 2 years, the primary end point occurred in 176 of 3714 women (4.75%) and in 477 of 12 254 men (3.90%) (unadjusted HR, 1.23; 95% CI, 1.03-1.46; **Figure 1**). After adjustment for baseline confounders, the risk of primary end point was no longer different between the sexes (adjusted HR, 1.00; 95% CI, 0.83-1.20). The risk of the secondary safety end point (BARC 3 or 5 bleeding) was higher in women (109 of 3714 [2.99%] vs 223 of 12 254 men [1.85%]; unadjusted HR, 1.63; 95% CI, 1.30-2.05; adjusted HR, 1.32; 95% CI, 1.04-1.67). Hemorrhagic stroke occurred more frequently in women (13 of 3714 [0.36%] vs 9 of 12 254 men [0.08%]; unadjusted HR, 4.81; 95% CI, 2.05-11.25; adjusted HR, 4.76; 95% CI, 1.92-11.81). There were no significant between-sex differences in the risk of MI, ischemic stroke, any revascularization, definite stent thrombosis, POCE, and NACE. The adjusted Cox regression analyses using different covariables showed consistent results (eTable 1 and eTable 2 in Supplement 1).

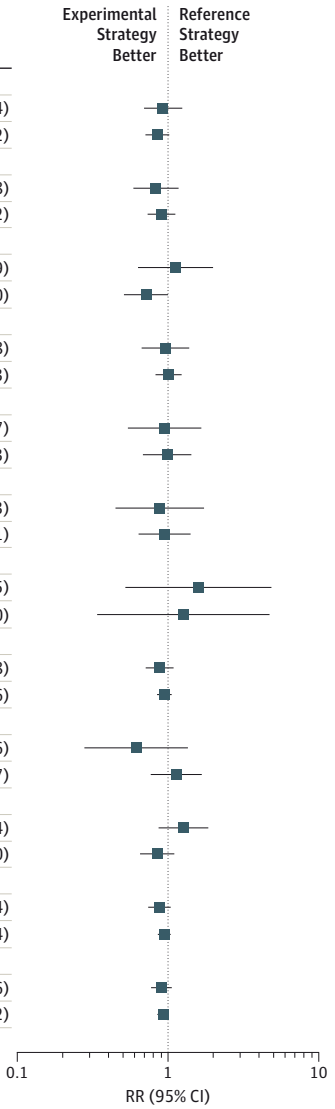
The higher rate of BARC 3 or 5 bleeding and hemorrhagic stroke in women was mainly observed in the period between the index procedure and 1 year (BARC 3 or 5 bleeding: 85 of 3714 women [2.32%] vs 168 of 12 254 men [1.39%]; adjusted HR, 1.36; 95% CI, 1.04-1.79; hemorrhagic stroke: 9 of 3714 women [0.25%] vs 6 of 12 254 men [0.05%]; adjusted HR, 4.99; 95% CI, 1.72-14.47) (eTable 3 in Supplement 1). From 1 to 2 years after PCI, the rate of BARC 3 or 5 bleeding, hemorrhagic stroke, and other outcomes were not different between sexes (eTable 4 in Supplement 1).

Association of Sex With Antiplatelet Strategy

The effect of experimental vs reference strategy on primary end point at 2 years was not different between the sexes (HR

Figure 2. Clinical Outcomes at 2 Years According to Sex and Antiplatelet Strategy

Outcomes at 2 y	Reference Strategy, No. (%)[a]	Experimental Strategy, No. (%)[a]	HR[b], exp/ref (95% CI)	P Value	P Value for Interaction
All-cause mortality or new Q-wave myocardial infarction					.63
Women	91 (4.93)	85 (4.56)	0.92 (0.69-1.24)	.60	
Men	258 (4.21)	219 (3.59)	0.85 (0.71-1.02)	.08	
All-cause mortality					.70
Women	71 (3.84)	60 (3.22)	0.83 (0.59-1.18)	.30	
Men	182 (2.97)	164 (2.68)	0.90 (0.73-1.12)	.35	
New Q-wave myocardial infarction					.19
Women	22 (1.22)	25 (1.37)	1.12 (0.63-1.99)	.69	
Men	81 (1.34)	58 (0.97)	0.72 (0.51-1.00)	.05	
Myocardial infarction					.81
Women	60 (3.33)	58 (3.18)	0.96 (0.67-1.38)	.82	
Men	190 (3.15)	190 (3.17)	1.01 (0.83-1.23)	.92	
Stroke overall					.91
Women	25 (1.39)	24 (1.31)	0.95 (0.54-1.67)	.86	
Men	57 (0.95)	56 (0.94)	0.99 (0.68-1.43)	.96	
Ischemic stroke					.86
Women	18 (1.00)	16 (0.88)	0.88 (0.45-1.73)	.71	
Men	50 (0.83)	47 (0.79)	0.95 (0.64-1.41)	.79	
Hemorrhagic stroke					.79
Women	5 (0.28)	8 (0.44)	1.59 (0.52-4.85)	.42	
Men	4 (0.07)	5 (0.08)	1.26 (0.34-4.70)	.73	
Any revascularization					.50
Women	182 (10.11)	162 (8.95)	0.87 (0.71-1.08)	.21	
Men	611 (10.13)	577 (9.65)	0.95 (0.85-1.06)	.38	
Definite stent thrombosis					.17
Women	16 (0.88)	10 (0.55)	0.62 (0.28-1.36)	.23	
Men	48 (0.79)	54 (0.90)	1.13 (0.77-1.67)	.53	
BARC 3 or 5 bleeding					.09
Women	48 (2.65)	61 (3.33)	1.26 (0.87-1.84)	.23	
Men	121 (2.00)	102 (1.70)	0.85 (0.65-1.10)	.22	
Patient-oriented composite end point					.45
Women	273 (14.94)	243 (13.23)	0.88 (0.74-1.04)	.14	
Men	858 (14.07)	807 (13.36)	0.95 (0.86-1.04)	.25	
Net adverse clinical events					.72
Women	303 (16.58)	277 (15.06)	0.90 (0.77-1.06)	.21	
Men	934 (15.31)	868 (14.37)	0.93 (0.85-1.02)	.14	



BARC indicates Bleeding Academic Research Consortium; HR, hazard ratio; RR, risk ratio.

[a] Data were analyzed using the unadjusted Kaplan-Meier method.

[b] Unadjusted hazard ratio between experimental (exp) vs reference (ref) strategy in each sex.

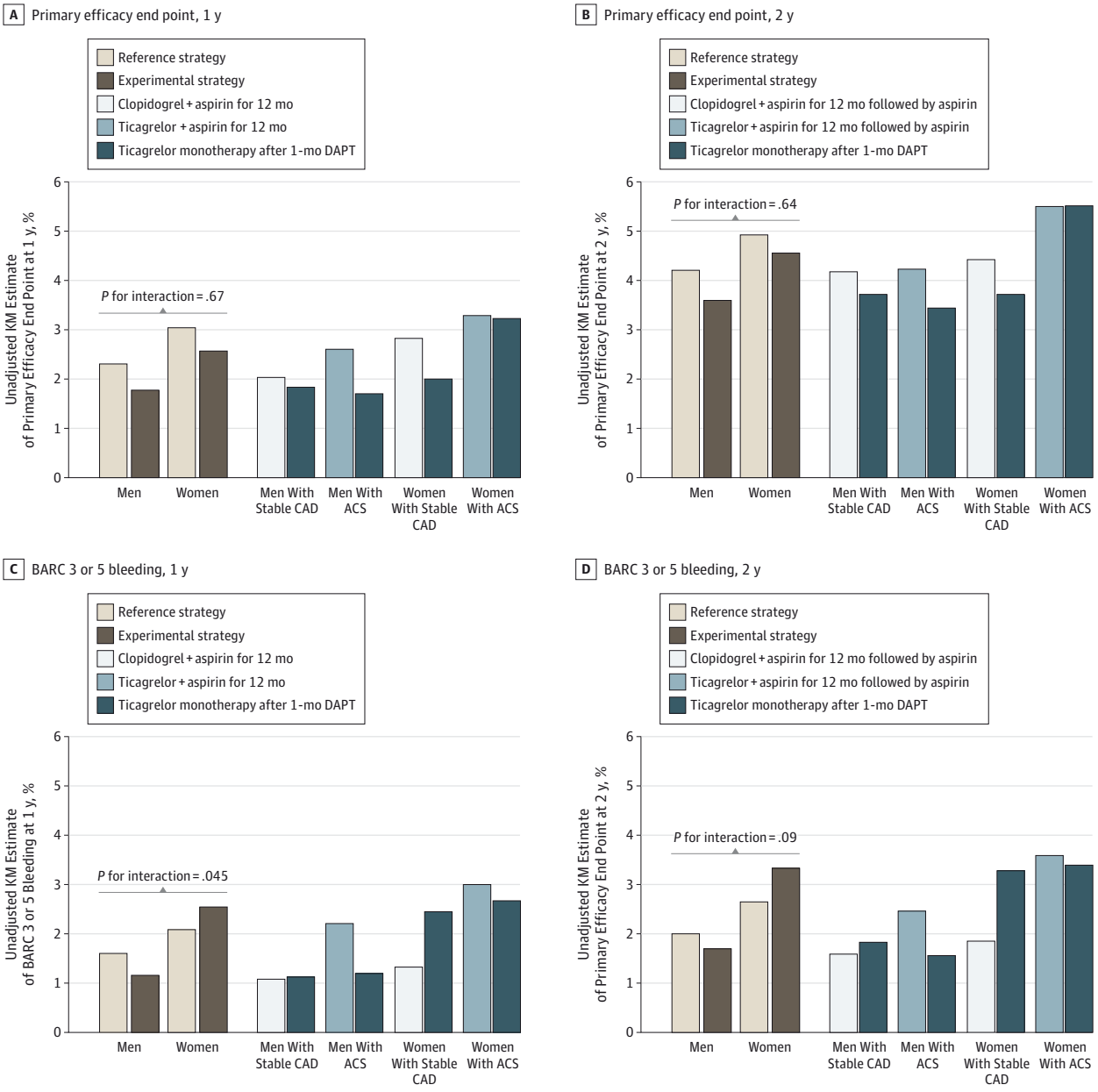
for men, 0.85; 95% CI, 0.71-1.02; HR for women, 0.92; 95% CI, 0.69-1.24; *P* for interaction = .63; **Figure 2**). Landmark analyses of the primary end point at 1 year and between 1 to 2 years showed no significant interaction between sex and antiplatelet strategies (eFigure 2 and eFigure 3 in Supplement 1).

No significant difference in the effect of antiplatelet strategy on secondary safety end point (BARC 3 or 5 bleeding) at 2 years between the sexes was observed (HR for men, 0.85; 95% CI, 0.65-1.10; HR for women, 1.26; 95% CI, 0.87-1.84; *P* for interaction = .09; Figure 2 and **Figure 3**). Compared with reference strategy, the experimental strategy was associated with a lower risk of BARC 3 or 5 bleeding at 1 year in men (HR, 0.72; 95% CI, 0.53-0.98) but not in women (HR, 1.23; 95% CI, 0.80-1.89, *P* for interaction = .045) (Figure 3; eFigure 2 in Supplement 1).

The effect of experimental and reference antiplatelet strategy on other outcomes at 2 years including investigator-reported MI, stroke, revascularization, definite stent thrombosis, POCE, and NACE were similar between the sexes (Figure 2). No significant interaction between antiplatelet strategies and sex with other outcomes at 1 year and between 1 and 2 years was demonstrated (eFigures 2 and 3 in Supplement 1).

Table 2 shows the rate of adherence to antiplatelet strategy at follow-up between women and men. The percentage of men and women adhering to their treatment strategy were similar at discharge and 1-month follow-up, whereas rates of adherence were higher in men from the 3-month follow-up to

Figure 3. Interaction Between Sex and Antiplatelet Strategy on Primary Efficacy and Secondary Safety End Point (Bleeding Academic Research Consortium [BARC] 3 or 5 Bleeding) at 1 and 2 Years



The x-axis shows the categories of the patients according to sex and clinical presentation, and the y-axis shows the unadjusted Kaplan-Meier (KM) estimate of primary efficacy end point (all-cause mortality or new Q-wave myocardial infarction) or secondary safety end point (BARC 3 or 5 bleeding) at 1 and 2 years after percutaneous coronary intervention. ACS indicates acute coronary syndrome; CAD, coronary artery disease; DAPT, dual antiplatelet therapy.

2 years. Compared with men, women had a lower rate of adherence to ticagrelor monotherapy at 18 months and 24 months after PCI, while at the same time adherence to aspirin monotherapy was similar between sexes (eTables 5 and 6 in Supplement 1). In patients who were allocated to ticagrelor treatment, the rate of dyspnea within 2 years was 18.17% in women (508 of 2796) and 14.71% in men (1370 of 9316) ($P < .001$). Among patients who were not adherent to antiplatelet strategy at 2 years, the rate of dyspnea was higher in women than men (193 of 570 [33.9%] vs 465 of 1625 [28.6%]; $P = .02$).

Discussion

In this prespecified subgroup analysis of the GLOBAL LEADERS study, the association of sex with clinical outcomes after PCI according to 2 different antiplatelet strategies was studied. The

Table 2. Adherence to Antiplatelet Strategy and Sex

Variable	No./Total No. (%)		
	Men (n = 12 254)	Women (n = 3714)	*P* Value[a]
Discharge	11 905/12 228 (97.4)	3603/3696 (97.5)	.72
Follow-up, mo			
1	11 519/11 938 (96.5)	3450/3596 (95.9)	.14
3	10 631/11 786 (90.2)	3136/3540 (88.6)	.006
6	10 418/11 701 (89)	3023/3506 (86.2)	<.001
12	10 008/11 590 (86.4)	2888/3493 (82.7)	<.001
18	9782/11 400 (85.8)	2858/3420 (83.6)	.001
24	9913/11 538 (85.9)	2878/3448 (83.5)	<.001

[a] *P* value derived from χ^2 test.

main findings are as follows. First, women experienced a similar risk of ischemic events compared with men at 2 years after PCI after adjustment for confounders. Second, women had a higher rate of hemorrhagic stroke and BARC 3 or 5 bleeding compared with men at 2 years after PCI, with the difference observed mainly during the first year after PCI. Third, there were no significant between-sex differences in the effect of the experimental and reference antiplatelet strategy on outcomes at 2 years after PCI. However, compared with reference strategy, the experimental strategy was associated with a lower risk of BARC 3 or 5 bleeding at 1 year in men but not in women (*P* for interaction = .045).

Early studies reported that women with CAD had a poorer prognosis than men.[17] Women treated for CAD are usually older and have higher prevalence of comorbidities that affect the outcomes.[2] After adjustment for the confounders, many studies have shown a comparable ischemic risk after PCI between men and women.[18-20] In addition, the sex gap in outcomes after revascularization has been attenuated by the efficacy and safety of DES, as demonstrated by several all-comer stent trials showing similar long-term outcomes between sexes after PCI.[6,9] In this study, women were older and had higher prevalence of diabetes, hypertension, and impaired renal function than men, and the unadjusted analysis shows the higher risk of primary end point and other ischemic outcomes in women. However, the differences were no longer evident in the adjusted models, suggesting that the differences in ischemic risk between women and men were attributed to confounders and not associated with sex per se. Furthermore, it could be speculated that the sex gap may have been diminished by contemporary PCI practice with the use of newer-generation DES, potent antiplatelet agents, and optimal medical therapy.

Regardless of sex, DAPT with aspirin and P2Y12 inhibitor has been the standard of care in patients treated with DES to prevent stent thrombosis and other ischemic events.[12] In patients with ACS, guidelines recommend potent P2Y12 inhibitors, such as ticagrelor or prasugrel, in combination with aspirin, given that they have been shown to reduce the risk of ischemic adverse events after revascularization.[21,22] However, this benefit comes at the expense of an increased bleeding risk.[23] Several studies have shown that women treated with antiplatelet therapy after PCI are at high risk of bleeding, and female sex is well recognized as an independent predictor for bleeding.[11,24] However, risk scores to predict bleeding after PCI, such as the PARIS bleeding risk[25] and PRECISE DAPT score,[26] did not identify any predictive value for female sex, and sex was not subsequently included in the risk model. Because both risk scores were developed in populations in which potent P2Y12 inhibitors were not widely used, it is unclear whether sex still affects the risk of bleeding after PCI.

This study reveals that women undergoing PCI are at higher risk of major bleeding and hemorrhagic stroke than men. This difference persists after adjustment for confounders, confirming that sex is an independent predictor for major bleeding after PCI. Therefore, our findings question the predictive ability of bleeding risk scores where sex is not included and emphasizes the need for external validation of bleeding risk scores in contemporary PCI practice.

The European Association of PCI survey in 2015 on DAPT in clinical practice revealed that sex is one of the variables physicians use to weigh the risks of bleeding vs ischemia after PCI with DES.[27] However, a 2017 meta-analysis[28] of randomized clinical trials has shown the comparable efficacy and safety of potent P2Y12 inhibitors between sexes, suggesting that the decision to use these agents should not rely on sex. Furthermore, guideline recommendations on the use of antiplatelet therapy after PCI are independent of sex.[12] However, we did observe an interaction between sex and antiplatelet strategy on bleeding at 1 year.

In the reference group of the GLOBAL LEADERS study, the P2Y12 inhibitor component of DAPT was dependent on clinical presentation; patients with stable CAD received clopidogrel while patients with ACS received ticagrelor. In the experimental group, both patients with stable CAD and patients with ACS received ticagrelor. The observed interaction between sex and antiplatelet strategy at 1 year was primarily driven by the experimental strategy in women with stable CAD (Figure 3). In women with stable CAD, the rate of BARC 3 or 5 bleeding associated with experimental strategy was almost 2 times higher than in the reference strategy, while in men with stable CAD, the rate was almost equal between the 2 strategies. Although the evidence supporting routine use of potent P2Y12 inhibitors in stable CAD is lacking, off-label prescription has been reported to be as high as 34%.[29] The 2017 European Society of Cardiology–focused update on DAPT gave class IIb recommendation for the consideration of potent P2Y12 inhibitor in patients with stable CAD undergoing PCI after taking into account the ischemic and bleeding risk.[30] Our study suggests

that potent P2Y12 inhibitors should be used with caution in women who present with stable CAD.

The lower rate of adherence to antiplatelet strategy in women compared with men found in this study is consistent with data from the PARIS registry where DAPT cessation was more common in women owing to disruption for bleeding or discontinuation due to noncompliance.[11] In the Bern PCI registry,[31] female sex was identified as an independent predictor for premature ticagrelor cessation, which was largely owing to bleeding or dyspnea. This observation should encourage physicians to carefully weigh the risk and benefit of using ticagrelor in women.

Limitations

First, the randomization in the GLOBAL LEADER study was not stratified by sex. Hence, the number of women enrolled in the study was lower than men, and the results are at risk for a type II error. Second, our analyses are considered exploratory, and statistical adjustment for multiple testing was not performed. Therefore, the difference in the effect of antiplatelet strategy on bleeding between sexes could be a play of chance and should be regarded as hypothesis-generating.[32] Finally, the trial did not have a clinical adjudication committee for serious adverse events owing to limited financial resources. The end points were site-reported with the exception of primary end point: all-cause death and new Q-wave MIs assessed by an independent ECG core laboratory. However, the trial was monitored for consistency, and reporting of events and on-site monitoring visits was regularly performed.

Conclusions

In an all-comers population undergoing contemporary PCI, the risk of all-cause mortality or new Q-wave MI at 2 years was similar between women and men. Nevertheless, women experienced higher risk of bleeding and hemorrhagic stroke compared with men. The effect of 2 antiplatelet strategies on death and Q-wave myocardial infarction following PCI did not differ between the sexes at 2 years.

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